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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/068,751	11/02/98	FRANZ W	690-110PCT

002292 HM12/0628
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EXAMINER	
SCHMIDT,M	
ART UNIT	PAPER NUMBER
1635	13

DATE MAILED: 06/28/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trad marks

Office Action Summary

Application No.	Applicant(s)
09/068,751	Frary et al.
Examiner	**Group Art Unit**
Schmidt	1635

—The MAILING DATE of this communication appears on the cover sheet beneath the correspondence address—

Peri d for Response

A SHORTENED STATUTORY PERIOD FOR RESPONSE IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a response be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for response specified above is less than thirty (30) days, a response within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for response is specified above, such period shall, by default, expire SIX (6) MONTHS from the mailing date of this communication .
- Failure to respond within the set or extended period for response will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).

Status

☑ Responsive to communication(s) filed on _____.

☒ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 1 1; 453 O.G. 213.

Disp sition of Claims

☒ Claim(s) 20-73 is/are pending in the application.

Of the above claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) 20-73 is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claim(s) _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119 (a)-(d)

☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 11 9(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 1 7.2(a)).

*Certified copies not received: _____.

Attachment(s)

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☒ Interview Summary, PTO-413

☐ Notice of References Cited, PTO-892

☐ Notice of Informal Patent Application, PTO-152

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Other _____

Office Action Summary

DETAILED ACTION

Claim Rejections - 35 USC § 101

1. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

2. Claims 45-51 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. The claims are drawn to "a heart tissue-specific regulatory nucleic acid sequence" comprising specific regulatory elements. The claim does not specify an isolated nucleic acid and as such reads on any such native sequences in a whole organism.

Claim Rejections - 35 USC § 112

3. Claims 20-51 and 53 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 20-51 and 53 contain the language "or a functional homolog of said regulatory elements" which is indefinite since the metes and bounds of the possible sequences having any functional correlation to the claimed regulatory sequences is not clear. Although the specification suggests the ability in the art to identify related sequences from other species of organisms, neither the art nor the specification clearly suggest the amount of functionality of such unknown sequences so as to classify them as "functional homologs."

Claim 38, line 7 contains a typographical error for "SEQ ID NOA;". It appears that the claim should read "SEQ ID NO: 1;".

4. New claims 40-44 and 69-73 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention, for the same reasons of record as set forth in the Official action mailed 10/14/99 pertaining to original claims 1-3.

Applicant's arguments filed 2/14/00 have been fully considered but they are not persuasive.

New claims 40-44 and 69-73 are drawn to pharmaceutical compositions and methods of delivery of a gene to a subject. The claims read broadly on gene therapy to any whole organism.

The previous claims had specified expression of antisense and ribozymes as a part of the "working model" having therapeutic functions. However, the claims as amended which are drawn to pharmaceutical compositions and methods of treatment do not specify antisense or ribozyme expression *per se*. Instead the claims more broadly encompass expression of any gene therapeutic product under the control of the claimed regulatory elements in whole organisms. Further the new claims specify expression of the claimed nucleic acid constructs from a viral vector and complexed with liposomes.

Applicant notes that there are difficulties in accomplishing successful gene therapy and that Anderson teaches the primary difficulties. For the sake of the present claims, it is reiterated

that Anderson specifically teaches the problems with development of viral vectors for delivery of gene therapeutic agents as "obtaining efficient delivery, transducing non-dividing cells, (and) sustaining long-term gene expression." (p. 25) Anderson further teaches the problems with targeting specific cells types and sustained delivery of the gene therapeutic product in these cells types. (See page 26 especially)

Applicants respond to the previous rejection by asserting that the present invention provides an effective delivery system for gene therapeutic applications. While Anderson specifically addresses one problem with using viral promoters for expression of the desired therapeutic genes, the examples taught in the instant specification do provide teaching that the instantly taught vectors overcome this problem and function to express a reporter gene when injected into mice, and do show tissue specific expression. However, this mode of delivery of the instant vector constructs, via injection to the desired cells, does not correlate to successful delivery of such constructs by other routes of delivery such that one skilled in the art would be able to make and use the invention as broadly claimed for any gene therapeutic application.

Specifically, neither the specification as filed nor the art teach guidelines for successful delivery of gene therapeutic constructs nor general formulations for delivery of any such construct as broadly claimed. The factors considered unpredictable are taught by Anderson above for making gene therapeutic constructs which function in whole organisms. Thus it would require undue experimentation to make and use the invention as claimed.

Claim Rejections - 35 USC § 102

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

6. Claims 20, 22-28, 33, 38 and 45-51 are rejected under 35 U.S.C. 102(b) as being anticipated by Franz et al.

Franz et al. teach a 2.1 kB fragment of the 5' flanking region of the rat cardiac MLC-2 gene fused to a firefly luciferase reporter gene. The 2.1kB MLC-2 fragment extends from +12 to -2700. Although Franz et al. may not specifically name the MLE1 element of the MLC-2 regulatory region, the sequence is taught and would inherently function the same way. Thus in view of the "comprising" and "functional homolog" language of the instant claims, Franz et al. reads on the claimed invention.

7. Claims 20, 22, 25-28, 33, 38, 45-46 and 49-51 are rejected under 35 U.S.C. 102(b) as being anticipated by Arnold et al.

Arnold et al. teach the chicken MLC-2A promoter-chloramphenicol acetyl transferase fusion construct for expression in chicken muscle cells. Thus in view of the "comprising" and "functional homolog" language of the instant claims, Arnold et al. reads on the claimed invention.

8. Claims 20, 22-28, 33, 38 and 45-51 are rejected under 35 U.S.C. 102(b) as being anticipated by Knowleton et al.

Knowleton et al. teach rat MLC-2 luciferase fusion constructs. Thus in view of the "comprising" and "functional homolog" language of the instant claims, Knowleton et al. reads on the claimed invention.

9. Claims 20, 22-28, 33, 38 and 45-51 are rejected under 35 U.S.C. 102(b) as being anticipated by Shubeita et al.

Shubeita et al. teach rat MLC-2 luciferase fusion constructs. Thus in view of the "comprising" and "functional homolog" language of the instant claims, Shubeita et al. reads on the claimed invention.

10. Claims 20-28, 33, 38 and 45-51 are rejected under 35 U.S.C. 102(b) as being anticipated by Navankasattusas et al.

Navankasattusas et al. teach specific elements of the MLC-2 having cardiac specific expression and encompass a teaching of the whole promoter. Thus in view of the "comprising" and "functional homolog" language of the instant claims, Navankasattus et al. reads on the claimed invention. Further, since Navankasattusas et al. teaches deletion of cardiac-specific regions of the MLC-2 promoter, in view of the "functional homolog" language, the art reads on claim 21.

11. Claims 20, 22-28, 33, 38 and 45-51 are rejected under 35 U.S.C. 102(b) as being anticipated by Thornburn et al.

Thornburn et al. teach rat MLC-2 luciferase fusion constructs. Thus in view of the "comprising" and "functional homolog" language of the instant claims, Thornburn et al. reads on the claimed invention.

12. Claims 20, 22-28, 33, 38 and 45-51 are rejected under 35 U.S.C. 102(b) as being anticipated by Goswami et al.

Goswami et al. teach an MLC-2-CAT fusion constructs. Thus in view of the "comprising" and "functional homolog" language of the instant claims, Goswami et al. reads on the claimed invention.

Claim Rejections - 35 USC § 103

13. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 20-39 and 45-68 are rejected under 35 U.S.C. 103 (a) as being unpatentable over any one of the following in the alternative: Franz et al., Arnold et al, Knowleton et al, Shubeita et al, Navankasattusas et al, Thornburn et al, or Goswami et al. in view of Ricigliano et al. And Zaia et al. for the same reasons of record as set forth in the previous Official action on the merits mailed 10/14/99.

Applicant's arguments filed 2/14/00 have been fully considered but they are not persuasive.

Applicant argues that a prima facie case of obviousness was not made since "none of the references discloses or suggests the specific combination of regulatory elements recited in claim 20." Applicant argues that the closest art is Franz et al, does not "specifically describe a MLE1 element... (and) ascribe(s) the heart-specific expression mostly to a CSS sequence, explaining that deletion of the CSS sequence results in expression of marker genes in skeletal muscle."

In response, SEQ ID No. 1 comprises the entire MLC1 promoter and specifically in view of the "comprising" and "functional homolog" language of the claims, the cited references all read on the claimed regulatory region.

Furthermore, the new claims encompass not only expression of antisense and/or ribozyme therapeutic agents, but also (1) claim expression of any gene product, including dystrophin, a beta-adrenergic receptor, or a nitric oxide synthetase and (2) claim expression of the MLC-2 promoter containing constructs from adenovirus vectors.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to *Mary M. Schmidt*, whose telephone number is (703) 308-4471.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, *George Elliott, Ph.D.* may be reached at (703) 308-4003.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

M. M. Schmidt
June 26, 2000

George C. Elliott

George C. Elliott, Ph.D.
Supervisory Patent Examiner
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